Updates in the Diagnosis of Chronic Pancreatitis

Current Approaches and New Possibilities

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KEYWORDS

• Chronic pancreatitis • Diagnosis • Diagnostic criteria • Imaging • Biomarkers
• Pancreatic function tests

KEY POINTS

- Current diagnostic algorithms diagnose definitive chronic pancreatitis (CP) based solely on imaging criteria, while probable CP requires imaging criteria, functional tests, and clinical features.
- Criteria for diagnosing early and non-calcific CP remain under debate and need validation through prospective trials.
- Morphology does not correlate well with symptoms or function, and there are no surrogate markers for staging severity and monitoring disease progression.

INTRODUCTION AND BACKGROUND

Chronic pancreatitis (CP) is a multifactorial progressive fibro-inflammatory condition with an incidence rate of 5 to 8 per 100,000 individuals and a prevalence of 42 to 73 per 100,000 in the United States.[1] Grouping CP into one "disease" has been largely abandoned, as there is such a wide variety of etiologies, morphologies, or age of onset. The TIGAR-O classification includes multiple proven and putative etiologies, which increasingly include genetic, toxic, autoimmune, recurrent acute and severe acute pancreatitis (AP), obstructive, and less and less, idiopathic causes (**Table 1**).[2,3] Traditionally linked to factors such as alcohol consumption, smoking, or specific genetic mutations, it often starts with repetitive episodes of painful pancreatitis.[4,5] The North American Pancreatitis Study 2 group reported that nearly 3-quarters of patients were diagnosed with AP prior to CP diagnosis.[6] Around 3% to 36% of individuals develop CP within 3 to 8 years after their first episode of AP.[7,8] Patients often experience the

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Table 1
Etiologies of chronic pancreatitis reported according to the TIGAR-O classification system

Category	Description
*T*oxic-metabolic	Factors such as alcohol, tobacco, hypercalcemia, and hyperlipidemia.
*I*diopathic	Refers to cases where no identifiable cause can be determined.
*G*enetic	Includes hereditary pancreatitis and mutations in genes such as *PRSS1*, *SPINK1*, *CFTR*, and *CTRC*.
*A*utoimmune	Chronic pancreatitis associated with autoimmune conditions, often characterized by elevated IgG4.
*R*ecurrent and severe acute pancreatitis	Typically (recurrent) episodes of acute pancreatitis that lead to chronic changes in the pancreas.
*O*bstructive	Includes conditions like pancreatic duct obstruction, pancreas divisum, and tumors causing ductal blockage.

From Etemad B, Whitcomb DC. Chronic pancreatitis: Diagnosis, classification, and new genetic developments. Gastroenterology. 2001;120(3):682-707. https://doi.org/10.1053/gast.2001.22586.

gradual onset of persistent, severe pain, marking the transition to CP.[9] Classic diagnostic signs include combination of ductal calcifications, dilatation, and parenchymal atrophy (**Fig. 1**), and it may or may not lead to complications such as pancreatic pseudocysts, biliary strictures, deficiencies in pancreatic exocrine or endocrine functions, and bone loss.[5] However, increasingly recognized with sophisticated imaging and function tests is the entity known as "minimal change" CP (MCCP). MCCP has been defined as a condition wherein patients have a typical pancreatic type of chronic abdominal pain with equivocal findings on imaging and subtle, focal histologic changes, including duct proliferation, duct complex formation, adenomatous nodules, acinar cell atrophy, and intralobular or periductal fibrosis.[10]

Because imaging severity correlates so poorly with symptomatology, and a substantial minority of patients with morphologically obvious CP may be completely asymptomatic, CP has been defined as a "syndrome" rather than a "disease".[11–13] The proposed new mechanistic definition describes CP as a pathologic fibroinflammatory syndrome of the pancreas in individuals with genetic, environmental,

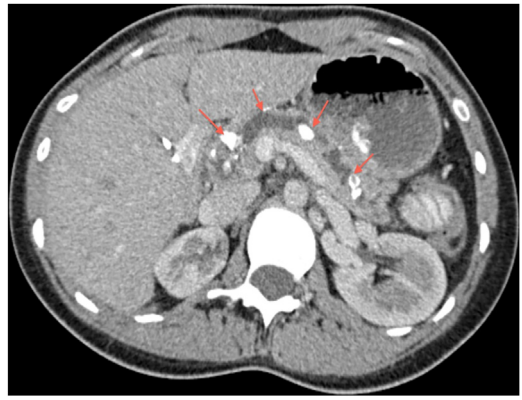

Fig. 1. Computed tomography (CT) scan showing multiple calcifications (*arrows*) in a dilated main pancreatic duct and in side branches.

and/or other risk factors who develop persistent pathologic responses to parenchymal injury or stress.[14]

Studies have shown that traditionally diagnosed CP patients face an elevated risk of pancreatic ductal adenocarcinoma (PDAC) in comparison to the general population.[15,16] Furthermore, CP is linked to a decreased quality-of-life, impacting mental health conditions adversely.[17] Currently, the management of CP is primarily directed at alleviating pain, addressing nutritional deficiencies, and treating structural complications that accompany the disease, partly due to the limited understanding of exact etiopathogenesis.[18] Interestingly, a significant portion of patients identified with CP report no pain (up to 30%[19]) and lack a history of AP, suggesting a potentially distinct disease with its unique pathogenesis.[20] In practice, "chronic pancreatitis" might be used broadly to encompass other chronic pancreatic inflammatory conditions that share similar features with, but are not entirely the same as, classic CP.[21]

In this review, we summarize the diagnostic evaluation of CP in adult patients, emphasizing the latest evidence and current approaches.

ADVANCES IN DIAGNOSTIC APPROACHES

Diagnosing CP continues to be a clinical challenge. At the core of the challenge is the lack of a true “gold standard”. Is it imaging, histology, or function? Must there be associated pain? Historic criteria were based on cases of advanced classic CP, characterized by pancreatic calcifications, significant ductal changes, and steatorrhea. These could not identify patients with MCCP. Traditional classification has been the Cambridge classification.[22] Guidelines from the American Pancreatic Association suggest its translational use for cross-sectional imaging interpretation, although its limitation is that it only acknowledges ductal changes.[23] To address this gap, the Consortium for the Study of Chronic Pancreatitis, Diabetes, and Pancreatic Cancer (CPDPC) have recently defined standardized features of CP on cross-sectional studies along with recommended reporting metrics.[24] Furthermore, the members of the International Association of Pancreatology, American Pancreatic Association, Japan Pancreas Society, and European Pancreatic Club have recently suggested consensus statements concerning early CP.[25] However, no consensus could be developed for its definition or diagnostic criteria. Notably, it has been agreed that the term “early” refers to the disease state, not its duration. In early CP, pancreatic function is preserved and features may be potentially reversible. Thus, diagnosis is possible with a combination of high-risk factors, appropriate clinical context, and supporting biomarkers.[25]

Currently, the diagnosis of CP involves a comprehensive evaluation of medical history, physical examination, laboratory tests, and imaging studies (**Box 1**,[26] **Fig. 2**). Importantly, achieving a high degree of certainty is crucial to prevent a false positive diagnosis, which can lead to social stigma and/or misdirected therapies associated with the label.

A practical diagnostic catalog was proposed in Japan’s 2009 evidence-based guidelines revised in 2015.[27] According to these criteria, CP can be diagnosed based on imaging alone if definitive imaging features are present. In cases where imaging suggests probable CP, patients should meet 2 out of 3 additional clinical criteria: repeated upper abdominal pain; abnormal serum or urine pancreatic enzyme concentrations; and abnormal pancreatic exocrine function. Typical histology, excluding PDAC, can also support the diagnosis, though obtaining biopsy samples is challenging.[28] The inclusion of suspected causes or risk factors in the diagnostic algorithm is still debated.[25,29] Risk factors such as alcohol abuse, smoking, or a family history with *PRSS1* mutation can increase the pretest probability of diagnosing the disease.

Box 1
University of Minnesota criteria for diagnosis of chronic pancreatitis

Characteristic chronic abdominal pain of greater than 6 mo duration and at least 1 of the following:

- Pancreatic calcifications on cross-sectional imaging.
- At least 2 of the following: greater than or equal to 4/9 criteria on EUS, compatible ductal or parenchymal abnormalities on secretin MRCP; abnormal endoscopic pancreatic function tests (peak HCO_3 $\leq$80 mM) or abnormal fecal elastase.
- Histopathology confirmed diagnosis of CP.
- Compatible clinical history and documented hereditary pancreatitis (*PRSS1* gene mutation).

Or

- History of unprovoked recurrent AP (multiple documented episodes of AP with characteristic pain associated with imaging diagnostic of AP and/or elevated serum amylase or lipase >3 times upper limit of normal, with ongoing intractable pain of same character).

Abbreviations: AP, acute pancreatitis; CP, chronic pancreatitis; EUS, endoscopic ultrasound; MRCP, magnetic resonance cholangiopancreatography.

Adapted from Bellin MD, Freeman ML, Schwarzenberg SJ, et al. Quality of Life Improves for Pediatric Patients After Total Pancreatectomy and Islet Autotransplant for Chronic Pancreatitis. Clinical Gastroenterology and Hepatology. 2011;9(9):793-799. https://doi.org/10.1016/j.cgh.2011.04.024.

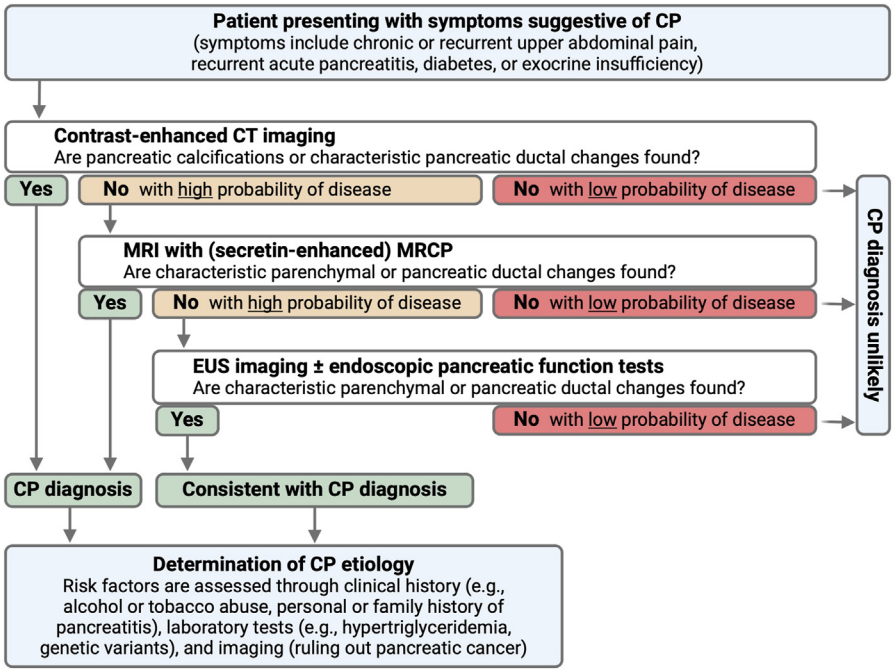

Fig. 2. Suggested algorithm for diagnosis of chronic pancreatitis; adapted from Singh and colleagues[1] CP, chronic pancreatitis; CT, computed tomography; EUS, endoscopic ultrasound; MRCP, magnetic resonance cholangiopancreatography; MRI, magnetic resonance imaging. Reproduced with permission from Singh VK, Yadav D, Garg PK. Diagnosis and Management of Chronic Pancreatitis: A Review. JAMA. 2019;322(24):2422. https://doi.org/10.1001/jama.2019.19411. Copyright © 2019 American Medical Association. All rights reserved, including those for text and data mining, AI training, and similar technologies.

However, since up to 20% of CP cases remain idiopathic, the absence of these risk factors should not exclude the diagnosis.[4]

Biomarkers

Currently, there are no established biomarkers for CP, although significant efforts are being made to identify circulating serum biomarkers to aid in diagnosis.[30–32] Existing research has investigated the diagnostic potential of individual proteins, as well as mRNA and metabolomic signatures, in the blood and urine of CP patients, but the studies were too small to yield definitive results.[4,33–36] However, a European group has recently identified and validated a plasma metabolome panel consisting of 8 markers.[37] In a cohort of 670 patients, from 4 centers, this panel successfully distinguished between CP and healthy controls, achieving an area under the curve (AUC) of 0.85 (95% confidence interval [CI] 0.79–0.91). Furthermore, neutrophil gelatinase-associated lipocalin (NGAL), a proinflammatory cytokine elevated during inflammation that binds fatty acids, has garnered significant attention as a promising CP biomarker.[31] Recent research from the CPDPC Consortium indicates that increased plasma NGAL and variations in NGAL+ peripheral blood mononuclear cells suggest an immune response shift, which could serve as biomarkers for CP.[38] Additionally, the interaction between fatty acids and NGAL offers insights into the metabolic pathophysiology, potentially enhancing the diagnostic classification of CP.

Unlike AP marked by elevated serum amylase and lipase levels, these enzymes typically do not rise in CP, even during flare-ups. This lack of enzyme elevation is attributed to the gradual loss of enzyme-producing pancreatic tissue over time.[39] Notably, a study on 2 independent cohorts found that low plasma amylase activity, rather than elevated levels, showed high specificity (0.94 for levels below 17.3 U/L) for diagnosing CP.[40] Functional tests can indicate exocrine pancreatic insufficiency (EPI), which usually occurs after about 90% of pancreatic acinar cells are destroyed.[41] Additionally, while autoimmune pancreatitis can evolve into CP, widespread antibody testing is not advised unless there is a family history or signs indicative of autoimmune pancreatitis.[42] Genetic testing is recommended for individuals with a significant family history of CP, symptoms suggestive of cystic fibrosis, or an early onset of the disease.[43]

Imaging

Imaging remains crucial in the diagnosis of CP due to the lack of serum biomarkers and the risks associated with pancreatic biopsies.[23] A recent meta-analysis of 43 cohort studies assessed the diagnostic effectiveness of computed tomography (CT), MRI, EUS, endoscopic retrograde cholangiopancreatography (ERCP), and transabdominal ultrasound for CP.[44] These findings were also incorporated into the European guidelines for the diagnosis and treatment of CP.[45,46] EUS and ERCP demonstrated the highest sensitivity for advanced CP, at 81% (95% CI 70%–89%) and 82% (95% CI 76%–87%), respectively. Transabdominal ultrasound showed the lowest sensitivity at 67% (95% CI 53%–78%). All techniques had a specificity of 90% or higher. Importantly, these studies were based on traditional definitions of morphologically obvious CP, and may not be relevant to patients with non-calcific CP. In studies comparing imaging with histopathology as the reference standard in patients undergoing total pancreatectomy with islet autotransplantation for intractably painful non-calcific CP, MRI with secretin-enhanced magnetic resonance cholangiopancreatography (MRCP) have shown the best correlation, while EUS had surprisingly poor correlation.[47–49] The American College of Gastroenterology guidelines for management of CP endorsed these comments.[18]

Current guidelines advise using cross-sectional imaging initially because it is more accessible and non-invasive.[18,45,46] Although accurate for advanced morphologic disease, EUS has poor sensitivity and specificity, especially in patients with MCCP.[49] The Rosemont criteria, although widely cited, were based on consensus rather than a gold standard.[50] EUS should be considered only if CT or MRI results are unclear.[51] ERCP should not be employed solely for diagnostic purposes (**Fig. 3**).[52] For improved visualization of pancreatic duct abnormalities, such as strictures, duct dilations, and wall irregularities, secretin MRCP is suggested for its safety, effectiveness, and enhanced sensitivity to early changes.[45,51] This modality also allows EPI detection through semiquantitative measurement of duodenal filling.[53,54]

The CPDPC Consortium is actively working on enhancing quantitative MRI techniques to utilize MRI's ability to detect changes in the pancreatic tissue's T1 relaxation time, which is affected by its protein content, and to measure extracellular volume indicative of fibrosis, as well as the presence of fat.[55,56] The goal is to refine MRI's capability to closely mimic tissue histology in diagnosing various stages of CP.[57] Notably, the recent MINIMAP study, the first prospective, multi-institutional study exploring the potential of parenchymal MRI features as imaging biomarkers for CP, evaluated key MRI parameters such as the T1-weighted signal intensity ratio of the pancreas (T1 score), arterial-to-venous enhancement ratio (AVR) during venous and delayed phases, and pancreas volume and diameters.[58,59] CP patients exhibited significantly lower T1 scores, reflecting fibrosis due to acinar cell loss (**Fig. 4**A, B), and significantly lower AVRs due to impaired hemodynamics; they also had smaller pancreas volumes and diameters compared to controls. AUCs for these individual parameters ranged from 0.66 to 0.79.[59] Additionally, the study evaluated 2 MRI models combining these parameters, achieving higher diagnostic performance compared to individual metrics after propensity-matching adjustments for covariates (AUCs of 0.92 and 0.93). The association between the loss of T1-weighted signal with the loss of acinar cells replaced by fibrosis has been also supported by previous studies that included surgical histopathology and reported a correlation of parenchymal MRI features with the degree of fibrosis.[47,57,60]

Furthermore, selected EUS-based techniques enhance the diagnostic yield for specific clinical queries—such as using contrast-enhanced EUS to differentiate between cystic and solid pancreatic mass lesions in CP—but require further prospective evaluation.[4,61] Pancreatic fibrosis leads to increased tissue stiffness, with studies

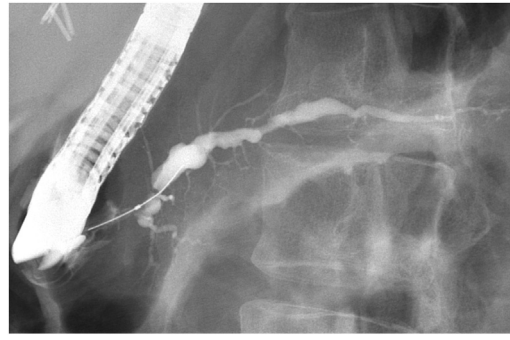

Fig. 3. Endoscopic retrograde cholangiopancreatography showing pancreas divisum with small duct chronic pancreatitis, featuring an irregular main pancreatic duct, diffuse stricturing, and abnormal side branches.

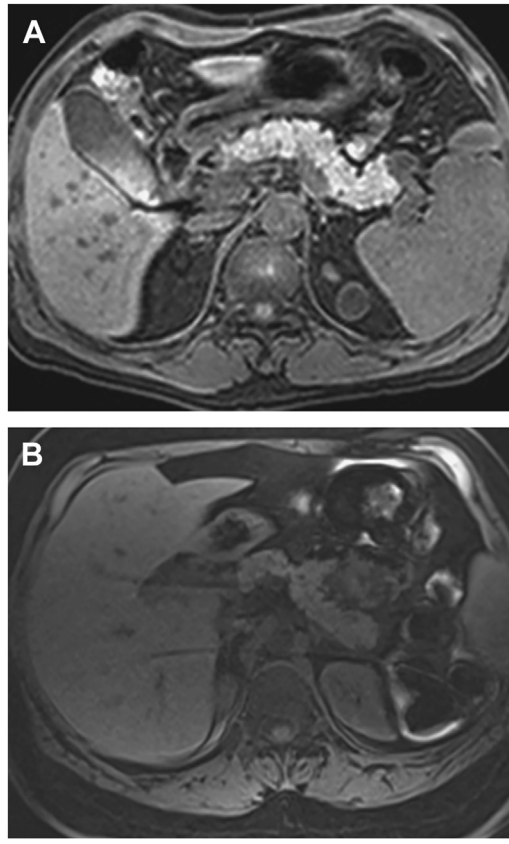

Fig. 4. MRI with normal and abnormal T1 signals. (*A*) Contrast-enhanced MRI showing uniformly homogenous and normal T1 signal. (*B*) Contrast-enhanced MRI showing decreased T1 signal in chronic pancreatitis.

consistently showing higher values in quantitative elastography of CP parenchyma compared to healthy controls.[62] Nonetheless, the diagnostic accuracy of EUS-based elastography does not yet surpass conventional EUS in CP and should be regarded as a complementary method.[63,64]

Pancreatic Function Testing

Insufficiency of the exocrine pancreas caused by the loss of functional acini, ductal epithelial dysfunction, ductal obstruction, or inactive pancreatic enzymes, can be observed in CP, AP, as well as PDAC. When other signs of CP are present, it supports the diagnosis and aids in staging the disease.[45] Clinically, it presents as bloating and diarrhea. Assessing fecal elastase-1 is a non-invasive, cost-effective, and commonly accessible test for evaluating the function of the exocrine pancreas. Though it may lack sensitivity for detecting mild to moderate EPI, it has a low risk of missing severe dysfunction.[45,65] Alternatively, the ^{13}C mixed triglyceride breath test is highly sensitive and, unlike fecal elastase-1 measurement, provides a functional readout, making it useful for gauging the effectiveness of treatment.[66–68] Additionally, measuring duodenal filling during secretin MRCP offers a semi-quantitative evaluation of exocrine

function and should be considered when MRCP is indicated for other reasons.[54] EPI can also be detected using secretin-stimulated collection of pancreatic juice during endoscopy, usually combined with EUS.[69] Importantly, it should to be identified early in the management process due to its association with malnutrition, micronutrient depletion, endocrine dysfunction, osteoporosis, and adverse cardiovascular events.[70–74]

Endocrine insufficiency related to CP can also develop. This type of diabetes is known as diabetes of the exocrine pancreas, pancreatogenic diabetes, or type 3c diabetes mellitus (T3cDM). Diabetes is estimated to affect between 25% and 80% of CP patients, usually developing 10 to 20 y after the diagnosis.[4] T3cDM, involving pancreatic islet dysfunction and loss due to exocrine pancreatic diseases, can be generally diagnosed if specific criteria are met: imaging shows pancreatic pathology, laboratory and/or clinical signs of EPI are present, and autoimmune markers for type 1 diabetes are absent.[75] To screen for T3cDM, both glycated hemoglobin A1c (HbA1c) and fasting glucose measurements are equally effective.

Disease Activity and Severity Scoring

Assessing the severity of CP remains challenging, as there are no established clinical scores or classification systems designed to predict short and medium-term outcomes.[45,52,76] The M-ANNHEIM classification and the Chronic Pancreatitis Prognosis Score (COPPS) are the only tools currently available that incorporate severity indices.[77,78] M-ANNHEIM, although developed based on expert opinions, identifies patients who may benefit from surgical or endoscopic interventions.[77,79,80] COPPS was developed using a comprehensive panel of clinical and laboratory parameters, prospectively correlated with an increased risk of hospitalization, assuming that hospital admission was a strong endpoint and an effective indicator of disease burden. The 5 parameters that best correlated (body mass index, HbA1c, C-reactive protein, platelet count, and pain intensity) were integrated into a numeric score, akin to the Child-Pugh Score in cirrhotic patients.[78] Notably, this score is currently undergoing a large-scale international validation.[81] Nevertheless, morphology correlates poorly with symptomatology in CP,[11,12] rendering any classification dependent on objective measurable findings of limited relevance to management.

Pancreatic Cancer Risk and Surveillance

Currently, there are no guidelines recommending systematic cancer screening in CP patients without a known familial component.[43,82] However, individuals with CP have an increased risk of PDAC, particularly in the initial years following diagnosis, and the incidence rates increase with CP disease duration.[16,83] Although alternating MRI and EUS are recommended for individuals with hereditary pancreatitis, there is no evidence to support their effectiveness or improved outcomes in this particular setting.[84] Additionally, CA 19-9 can be inaccurately elevated in patients with CP, rendering it ineffective for screening purposes.[5]

The relationship between CP and PDAC is intricate, as shared risk factors and the progression of the disease influence the likelihood of malignant transformation. Patients with CP do face a higher risk of developing PDAC compared to general population. A recent meta-analysis reported a relative risk ranging from 6.09 (95% CI 3.79–9.79) to 11.77 (95% CI 6.88–20.12).[83] However, the calculated risk may be confounded by smoking, an independent risk factor.[15] Individuals with hereditary pancreatitis face a significantly increased risk, which can be up to 70-fold that of the general population.[85,86] Irrespective of gene-carrier status, it is recommended that patients with hereditary pancreatitis participate in a screening program starting

at age 40, or 20 y after their diagnosis.[87] Furthermore, newly diagnosed diabetes may be an early sign of PDAC and warrants further testing in all CP patients.[82]

SUMMARY

Current diagnostic algorithms can diagnose definitive CP based solely on imaging criteria, while probable CP requires both imaging criteria and clinical features. The criteria for diagnosing early CP are still under debate and need validation through prospective trials. Additionally, there is no evidence that morphology follows function, and no surrogate markers exist for staging severity.

In conclusion, despite significant advancements in imaging techniques and diagnostic tests, challenges remain due to the lack of reliable tools for early diagnosis and assessment of disease activity.

CLINICS CARE POINTS

- Abdominal pain, manifesting in various patterns, is the fundamental symptom in patients with CP. Nevertheless, imaging severity correlates poorly with symptomatology, and a substantial minority of patients with morphologically obvious CP may be completely asymptomatic.
- Cross-sectional imaging should be used initially, with EUS reserved for cases where CT or MRI results are inconclusive or when planning biopsy or therapeutic interventions. Secretin MRCP is suggested for enhanced sensitivity to early changes.
- Classic diagnostic signs of CP include ductal calcifications, dilatation, and parenchymal atrophy. However, MCCP is increasingly recognized through advanced imaging and function tests.
- Patients with CP are at an increased risk of malignancy, although there is currently no effective strategy for early detection of PDAC in this patient population.

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DISCLOSURES

The authors have nothing to disclose.

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